Exhibit A

Bioabsorbable Polymers

Catgut suture - known in AD 150 in the time of Galen, who built his reputation by treating wounded gladiators.

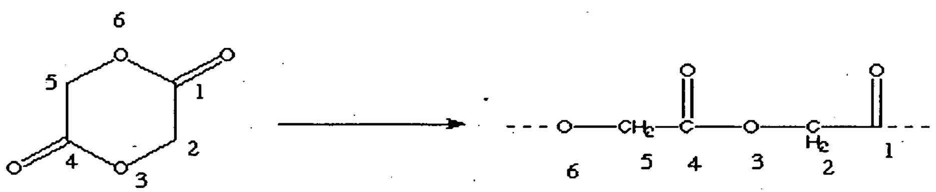
Enzymatic degradation results in foreign material which can serve as a nidus for infection or in urinary tract calcification.

Siliconized catgut (SICAT) is absorbed more rapidly than plain catgut yet retains its initial strength slightly longer. The silicone treatment also prevents the suture from drying out upon exposure to air.

Chromic catgut (Lister - yes that one...) obtained by treatment of catgut with chromium trioxide, a process used in tanning leather. This treatment slows the rate of absorption.

Polyglycolic acid (PGA)

Totally synthetic absorbable polymers (1970) clinical introduction of polyglycolic acid suture (Dexon, Davis and Geck, USA).



Glycolide - Dimer of Glycolic acid

Polyglycolic Acid

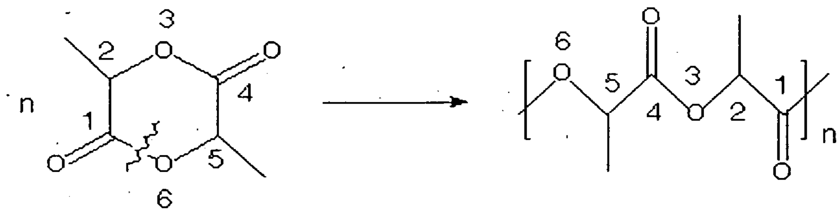
Advantages of synthetic materials:

Control over uniformity and mechanical properties.

Histological response to synthetic polymer generally predictable whereas reaction to non-synthetic materials (catgut) is variable and may produces a more intense inflammatory reaction.

Polylactic acid

PLA or polylactide, is prepared from the cyclic diester of lactic acid (lactide) by ring opening polymerization as shown below:



Lactic acid exists as two optical isomers or enantiomers. The L-enantiomer occurs in nature, a D,L racemic mixture results from the synthetic preparation of lactic acid.

Fibers spun from "L" polylactide (mp. 170 C) have high crystallinity when drawn whereas fibers spun from poly DL-lactide are amorphous.

Crystalline poly-L-lactide more resistant to hydrolytic degradation than the amorphous DL form.

The rate of poly-L-lactide degradation has been increased by plasticization with triethyl citrate, but this produced a less crystalline, more flexible material.

Time required for poly-L-lactide implants to be absorbed is relatively long and depends on polymer quality, processing conditions, implant site, and physical dimensions of the implant. Absorption time of about 1.5 years for 50 to 90 mg samples of radiolabelled poly-DL-lactide implanted in the abdominal walls of rats. Pure poly-L-lactide bone plates attached to sheep femora showed mechanical deterioration but little evidence of mass loss after four years. In the case of the radiolabelled implants, metabolism resulted in excretion primarily via respiration (CO2).

High molecular weight polymer can be prepared. Fiber samples with large tensile strength are available, by hot-drawing filaments spun from solution. Exposure of polylactic acid to gamma radiation has been shown to result in a decrease in MW.

Unlike PLA (absorbed slowly), PGA is absorbed within a few months postimplantation due to greater hydrolytic susceptibility. *In vitro* experiments have shown an effect on degradation by enzymes, buffer, pH, annealing treatments, and gamma irradiation.

Since PGA is susceptibility to degradation from moisture and gamma rays, use low humidity ethylene oxide gas sterilization procedures and moisture-proof packaging. Acceleration of in vivo degradation due to gamma irradiation has been exploited to create devices where early fragmentation is desired.

When Nature gives you lemons, make lemonade...

Copolymers of PGA/PLA can be tailored for a variety of applications: Poly(lactide-co-glycolide)

1. 90/10 PGA/PLA- first clinical material (Vicryl, Ethicon) for this type. Braided absorbable suture is similar to PGA. Both absorb between 90 and 120 days post implant. Vicryl retained strength slightly longer and was absorbed sooner than polyglycolide. Differences probably due to differences in polymer morphology because the amorphous regions of poly(lactide-co-glycolide) are more susceptible to hydrolytic attack than the crystalline regions.

Like pure PGA and pure PLA, the 90/10 PGA/PLA is also weakened by gamma irradiation.

Copolymers are amorphous between the compositional range 25 to 70 mole percent glycolide. Pure polyglycolide is about 50% crystalline, whereas pure poly-L-lactide is reported to be about 37% crystalline.

Surgical Clips and Staples

Injection molded staples : 70/30 L-lactide/glycolide copolymer (Lactomer - US Surgical).

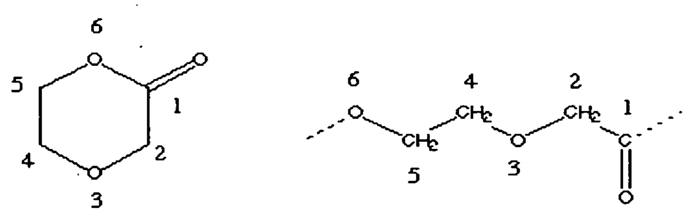
Poly(lactide-co-glycolide) polymers typically random.

Another approach to copolymerization: starting monomer is neither lactide nor glycolide, but rather the unsymmetrical cyclic diester containing one lactate and one glycolate moiety. This monomer gave a polymer with the same empirical formula as poly(lactide-co-50%-glycolide) but different properties due to a more stereoregular configuration.

Polydioxanone

Fibers made from polymers containing a high percentage of polyglycolide are too stiff for monofilament suture and thus are available only in braided form above the micro-suture size range. The first clinically tested mono-filament synthetic absorbable suture was made from polydioxanone (PDS, Ethicon).

The monomer p-dioxanone, is analogous to glycolide but yields a poly-(ether-ester) as shown below:

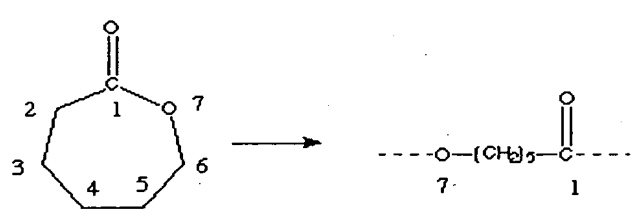


p-dioxanone Polydioxanone

Polydioxanone monofilament fibers retained tensile strength longer than the braided polyglycolide and were absorbed in about six months with minimal tissue response. Polydioxanone degradation in vitro was affected by gamma irradiation dosage but not substantially by the presence of enzymes.

Polycaprolactone

Polycaprolactone is synthesized from e-caprolactone as shown below:



ε-Caprolactone
lactone = inner ester

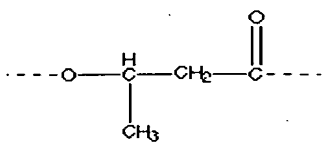
Polycaprolactone

This semi-crystalline polymer absorbed very slowly in vivo and released e-hydroxycaproic acid

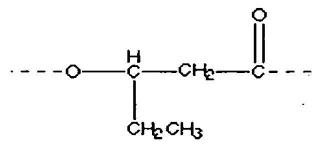
as the sole metabolite. Nonenzymatic bulk hydrolysis of ester linkages followed by fragmentation and release of oligomeric species. Fragments ultimately scavenged by macrophages and giant cells. Amorphous regions of the polymer are degraded prior to breakdown of the crystalline regions.

Copolymers of e-caprolactone and L-lactide are elastomeric when prepared from 25% e-caprolactone, 75% L-lactide and rigid when prepared from 10% e-caprolactone, 90% L-lactide.

Polyhydroxybutyrate



Polyhydroxybutyrate



Polyhydroxyvalerate

Poly-β-hydroxybutyrate (PHB) is a rare example of a biodegradable polymer that both occurs in nature and can easily be synthesized in vitro. Synthetic PHB, however, has not shown the stereoregularity found in the natural product. High MW, crystalline, and optically active PHB has been extracted from bacteria. This polymer is melt processable and has been proposed for use as absorbable suture.

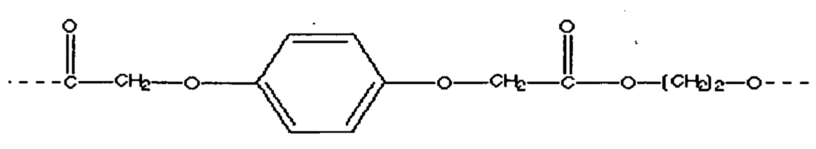
However, recent improvements in the extraction process have resulted in renewed interest in PHB for both medical and nonmedical applications. Copolymers of hydroxybutyrate and hydroxyvalerate (Biopol) have been developed to provide a wide variety of mechanical properties and more rapid degradation than can be achieved with pure PHB.

In general, an understanding of polymer morphology and crystallization behavior is important for optimization of processing conditions to achieve specific performance characteristics. Investigations into the morphology and crystallinity of Biopol copolymers have revealed isodimorphism, i.e. two crystalline phases were detected in the polymers each containing both types of repeating units.

Other Polyesters

Synthetic absorbable polyesters suffer from loss of mechanical properties upon sterilization with gamma irradiation. Yet poly(ethylene terephthalate) - Dacron - is a polyester that is resistant to gamma radiation induced degradation.

Thus a polyester analogous to Dacron containing glycolate ester linkages was synthesized as a gamma radiation resistant absorbable polymer shown below:



This polymer was copolymerized with glycolide to produce a fiber containing 90% polyglycolide which was significantly more resistant to gamma radiation induced strength loss than a pure polyglycolide fiber. A similar copolymer has been prepared using dioxanone instead of glycolide to improve the gamma radiation stability of polydioxanone

Poly(amino acids)

The use of amino acids as building blocks for synthetic absorbable polymers would seem logical. But synthesis and processing of such materials present difficulties.

Attachment of methotrexate to poly-L-lysine enhanced transport into the cells where the drug was released due to degradation of the poly(amino acid) moiety by lysosomal enzymes. Enzymatically degradable synthetic peptides have also been used to form crosslinks in drug releasing synthetic hydrogels. These hydrogel implants would otherwise be nondegradable if standard chemical crosslinking methods were employed.

Applications

Sutures (discussed)

Staples (discussed)

Mesh

Polyglycolic acid (Dexon) mesh is a recent innovation in wound closure severely injured spleen. the mesh was stretched and sutured over the injured surface.

Orthopedics

Fracture Fixation

The idea of using polyglycolic acid for fracture fixation plates and screws was patented in 1973 shortly after the introduction of the first synthetic absorbable suture. Advantages over steel plates and screws would be a reduction in excessive stress protection and elimination of a subsequent operation for removal. Not currently a clinical reality, but continuing experimentation has resulted in higher strength, higher modulus absorbable materials.

High MW polylactide,

polylactide reinforced with dissolvable calcium metaphosphate glass fibers

polylactide reinforced with polyglycolic acid fibers.

Bone Augmentation

Defects in bone caused by trauma or tumor removal often require autologous bone grafts. Ideally a synthetic substitute that induces the formation of new bone could obviate the need for sacrificing a normal bone from donor sites.

The role of synthetic absorbable polymers in this area is to provide a matrix and slow release depot for osteoinductive biological agents.

Poly(lactideglycolide) copolymers are compatible with new bone growth and have been patented in combination with various active ingredients which include demineralized bone, a purified bone morphogenic protein, and a proteolipid. Low molecular weight polylactide has also been combined with hydroxyapatite for use as an artificial bone filler.

Ligament Reconstruction

Medial collateral ligaments were removed from the knees of dogs and rabbits and replaced with woven poly(glycolide-co-10%lactide) prostheses. These implants served as a scaffold for the growth of ligament-like tissue which surpassed the strength of natural ligaments after six months.

Braided polyglycolic acid has been used to provide reinforcement for repair of the anterior cruciate ligament in dogs.

Dentistry

Tooth extraction frequently results in a "dry socket" in which delayed healing is accompanied by severe pain. A porous form of polylactic acid (Drylac, Osmed, USA) can be cut to size and implanted in the socket to eliminate this complication by filling the void, reducing hemorrhage, and providing a scaffold for tissue growth and repair.

Surgery

Ligating clips

Typically metal, but ideally made of absorbable material to eliminate their presence as a permanent foreign body and to prevent interference with computerized tomography scans. Clips made of both poly(lactide-co-30%-glycolide) (Lactomer, US Surgical, USA) and poly dioxanone (PDS, Ethicon, USA).

Vascular grafts

The concept of a graft which provides a scaffold for regeneration and is at least partially absorbable has been proposed by several authors. Materials that have been investigated include mixtures of polyurethane and polylactic acid, a woven mixture of Dacron and poly(DL-lactide) fibers, a woven mixture of Dacron and poly(L-lactide-co-90%-glycolide) fibers and a knitted mixture of Dacron and polyglycolic acid fibers.

Pure absorbable poly(glycolide-co-10%-lactide) fabric has been used experimentally as a patch material on the aortas of growing piglets.

Other uses

Polyglycolic acid tubing has been used experimentally as an external cuff to reinforce microarterial anastomoses. The cuff reducing the number of sutures required.

Intestinal Surgery

Bowel anastomosis, like vascular anastomosis, has inspired the invention of many sutureless devices to avoid the skill and time required to perform suture techniques. Although modern stapling equipment has reduced operating time, an absorbable device that works equally well would be an ideal approach.

Urology

Anastomosis of the ureter is often accomplished with the aid of a tubular, silicone rubber stent to facilitate accurate suture placement, provide adequate lumen for regeneration of epithelium and minimize urinary extravation. The use of absorbable polyglycolic acid stents in uretro-ureterostomies has been performed successfully in dogs. Although less flexible, the polyglycolic

acid tubes gave results equivalent to silicone rubber but absorbed in seven days and thus obviated the need for any additional procedure to remove the stent.

Nerve Repair

Sutureless anastomosis

Fibrous polyglycolic acid was used to fabricate a longitudinally open, porous, rough surfaced tube by a nonwoven processing technique. This device was evaluated in the repair of transected median nerves in monkeys. The absorbable device provided a rapid method of repairing nerves without the use of suture or operating microscope and gave results equivalent to those obtained in control nerves repaired by standard micro-surgical methods.

Nerve growth conduits

Peripheral nerve injuries often result in a gap which cannot be repaired without the use of an autogenous graft. Since nerve grafting requires the sacrifice of a normal sensory nerve, such as the sural nerve, the use of synthetic absorbable conduits has been investigated. Thus small gaps (less than 10 mm) in rabbit tibial nerve and mouse sciatic nerve have been bridged by growing axons in 90:10 glycolide:lactide copolymer mesh tubes and polylactide tubes, respectively.

Although neither absorbable nor nonabsorbable tubes at present have been shown capable of supporting nerve growth over long distances, the potential for regrowth is known to exist. For example, regrowth of the ulnar nerve in adult baboons across a 3 cm gap has been demonstrated using a vascularized, preformed pseudosynovial sheath.

Discussion

Most synthetic polymers used in medicine today were chosen from materials that are commercially available. Recall the fuss that Ratner made about new polymeric materials.

Synthetic absorbable polymers have no history of industrial use and thus were perfected solely for their medical applications.

The introduction of absorbable biopolymers demonstrates that new polymers can be created to meet the performance requirements of new devices and to displace the use of nonabsorbable polymers and metals. This trend is certain to continue. Just as the lactide-glycolide polymers are achieving greater clinical acceptance in various forms at present, other polymers will emerge further to extend the utility and indications for absorbable devices.
